GLAUCOMA IN FOCUS
Growing understanding of disease processes offers hope of better treatments
by Roibeard O’hEineachain

Glaucoma is a disease whose aetiology remains unknown, whose pathophysiology is poorly understood and whose diagnosis is often uncertain until it has progressed to the point that changes are occurring in patients’ vision. Yet research continues to shed light on the mysterious condition and bring hope of improved treatments and better outcomes for patients.

According to the World Health Organization (WHO), glaucoma is the leading cause of preventable irreversible blindness worldwide. Roughly 70 million of the world’s population are affected by glaucoma, and according to most epidemiological studies, 50 per cent are undiagnosed. Population studies indicate that around 10 per cent of patients diagnosed with glaucoma will go blind unilaterally and 20 per cent will go blind unilaterally after 20 years.

The ageing of the European population makes the need for improved diagnosis and treatment for glaucoma all the more urgent, Keith Barton MD, FRCP, FRCS, Moorfields Eye Hospital, London, UK, told *EuroTimes* in an interview.

The prevalence of glaucoma is roughly one per cent among people aged 40 years, four per cent among people aged 80 years. According to current projections, one third of the European population will be over 65 years old by the year 2050, and around 10 per cent will be over 80 years old, he said, adding: “These are the people who are going to be getting glaucoma and countries with relatively few hospitals are going to be overwhelmed by people. Health purchasers will see this as an impetus to change the way things are being done, with more and more patients being moved out of hospitals into clinics. However, we may find in the end that while it is laudable to bring care into the community in this way, in order to be efficient and less expensive, to have satellite clinics dealing with high volumes of patients networked with local hospitals using a central database,” he added.

**Diagnosis by structure and function.** The technologies used for diagnosing glaucoma are in general designed to detect either structural changes in the optic nerve or functional changes in terms of a reduced visual field. However, there are numerous factors that limit the confidence with which glaucoma specialists can determine either of those findings in early disease.

The structural tests range from the ‘gold standard’ stereo optic disc photograph to the more objective technologies that are quickly gaining acceptance in the glaucoma specialist’s diagnostic armamentarium. Those technologies include the Heidelberg Retinal Tomograph (HRT, Heidelberg engineering) which is a scanning laser ophthalmoscope and the GDx Nerve Fiber Analyzer (Carl Zeiss Meditec), which is a scanning laser polarimeter. There are also optical coherence tomographers such as the Stratus OCT (Carl Zeiss Meditec) which is fast becoming obsolete, and the more modern spectral-domain OCTs (Carl Zeiss Meditec, Optovue, Heidelberg Engineering, Topcon). All of the devices are designed to provide objective measurements of the optic nerve and/or the peripapillary region and all have accompanying software for comparing their measurements with normative databases.

“In published literature, there is little difference in the diagnostic precision between instruments, but in general the OCTs tend to do slightly better than HRT and GDx,” David Garway-Heath MD, Moorfields Eye Hospital, London, UK.

Matching structure to function
There is a clear correspondence between structure and function across the spectrum of glaucoma. However, in many of the larger studies that have charted glaucoma progression over several years, structural changes have occurred before detectable visual field changes and vice versa, with only a small overlap where both structure and function change together. This apparent discrepancy may result from measurement artefacts from the relatively short follow-up of the studies compared to the sometimes decades-long disease process of glaucoma, Dr Garway-Health told *EuroTimes*. Numerous factors can weaken the
association between structure and function in the short term, including factors that are unrelated or indirectly related to neuronal loss in the optic nerve head, he said. “Factors other than retinal ganglion cell number can cause changes in both structure and function. For example, visual field tests can be confounded by media opacity from cataract, retinal pathology, and subject inattention during the test. Similarly, retinal nerve fibre layer measurements may contain non-axonal tissue, such as glial tissue and blood vessels, and neuroretinal rim measurements in the optic nerve head, in addition to containing non-axonal components, may be affected by glaucomatous changes to the lamina cribrosa,” he added.

Retinal anatomy needs to be considered when relating structure and function measurements. Although an average map relating visual field test locations to optic nerve head sectors (Garway-Heath et al., *Ophthalmology*. 2000:107(10):1809-15) performs well, individuals may vary from each other in the precise retina/optic nerve head correspondence. New techniques to predict visual function from structure measurements, RNFL thickness (RNFLT) measurements from GDxVCC, has shown good results diagnose glaucoma (Zhu et al, IOVS 2010).

“The technique may enable structure and function measurements to be used together more effectively in the clinical routine, both to diagnose glaucoma and monitor its progression, something that it difficult at present. The same technique can be used to assess structure/function concordance (Zhu et al Arch Ophthalmol 2011, in press), which can highlight to clinicians good (concordant) and poor (discordant) data,” he said.

IOP a moving target Currently, all treatments for glaucoma are aimed at reducing IOP. The results of several large studies indicate that reducing IOP in patients with ocular hypertension and glaucoma significantly reduced the risk of glaucomatous changes to the optic nerve or changes in the visual field. The studies have also shifted the goalposts with regard to the level of IOP reduction that physicians should aim for.

For example, in the Ocular Hypertension Treatment Study (OHTS) the patients in the medication group had received therapy adequate to reduce IOP to 25 mmHg or lower and by at least 20 per cent from baseline. However, the results of the Advanced Glaucoma Intervention Study (AGIS) indicate that an IOP below 18.0 mmHg is a more effective target. Moreover, the results of the Early Manifest Glaucoma Trial (EMGT) indicated that the risk of disease progression could be reduced by 10 per cent for every 1.0 mmHg of IOP reduction.

Accurate measuring and monitoring of IOP is therefore essential for titrating therapy and assessing treatment efficacy. However, current approaches to IOP measurement and monitoring may fall short of the standard necessary to determine a patient’s true level of IOP control. Robert N Weinreb MD, told EuroTimes in an interview.

“Clinical management at the current time consists of a single measurement of intraocular pressure in the office which means that the vast majority of the time the level of IOP is not known. We have demonstrated in several studies that peak IOP occurs outside of office hours in at least two thirds of healthy patients and glaucoma patients,” said Dr Weinreb, University of California, San Diego, La Jolla, California. As a result, the peak IOP of many patients with glaucoma would go undetected, and could only be ascertained with 24-hour monitoring. To that end there are now several technologies under development such as contact lens-based and implantable devices, and self-tonometry devices are already available in clinical investigations.

“The prospect of 24-hour monitoring gives us the opportunity to personalise IOP measurement,” he said.

Dr Weinreb noted that variations among glaucoma patients in terms of their 24-hour IOP patterns could have very important clinical implications. The different pharmacologic agents and surgical procedures used for controlling IOP in glaucoma patients have different effects on 24-hour pressure, he said. He pointed out that while the prostaglandin analogues and carbonic anhydrase inhibitors are effective in controlling IOP at day and night, the beta-blockers and alpha agonists are only effective during the day.

He added that 24-hour monitoring could reveal important clues regarding what aspects of IOP are more important in the glaucoma disease process.

“At the current time we don’t fully understand the relationship between IOP and the progression to glaucoma. By being able to have a broader understanding of IOP throughout the 24 hour day we should be able to ascertain which IOP parameters are most relevant and are the ones that are most important to treat, whether it is the peak IOP, mean IOP, the area under the curve, the degree of variation, or all of them,” Dr Weinreb said.

Research in recent years has revealed additional risk factors for glaucomatous disease, he noted. They include ocular perfusion pressure, which is calculated by subtracting IOP from systemic blood pressure, and intracranial pressure, which is derived from cerebral spinal fluid pressure measured through lumbar punctures. These findings may help explain why the condition progresses in some patients despite good IOP control, Dr Weinreb added.

“There appears to be a pressure dependent component in some patients and a pressure independent component in some patients. That is one of the reasons why the concept of neuroprotection, a treatment independent of IOP, to reduce glaucoma progression is so interesting,” he said.

Trabeculectomy a less predictable option The introduction of prostaglandin analogues appears to have greatly reduced the need for surgery, however, for various reasons IOP remains elevated despite maximal therapy and when this occurs surgery becomes the chief option.

The current surgery of choice is trabeculectomy, a procedure that, with a few modifications, is over a century old. It is the standard surgical treatment for open-angle glaucoma because most glaucoma surgeons find it is the most reliable means of bringing IOP down to target levels. However, the technique is not without its drawbacks. Because of its invasive nature it can...
induce a high rate of cataract progression, flat anterior chambers leaking blebs and hypotony maculopathy and endophthalmitis rates up to 1.0 per cent.

There are several alternative penetrating techniques available to surgeons which appear to result in similar reductions of IOP with fewer complications. For example, in the Tube vs. trabeculectomy study, the trabeculectomy group had significantly lower mean IOPs than the tube group during the first three months, but there was no difference afterwards.

In addition, surgery with the Baerveldt tube resulted in a significantly lower failure rate than trabeculectomy (3.9 per cent vs. 13.5 per cent). Furthermore, significantly more patients in the trabeculectomy group (57 per cent) experienced postoperative complications than those in the tube group (34 per cent) during the first year of follow-up (p = 0.001).

In order to reduce the risk of hypotony, tubes can be constricted, with an absorbable or releasable suture or fitted with a minimum pressure controlling valve, as in the Ahmed valve. In addition, non-penetrating techniques such as deep-sclerectomy, reduce the risk of hypotony by draining aqueous via a Descemet’s membrane which separates the anterior chamber from the sclerectomy flap. “It should be remembered, however, that trabeculectomy, tubes, valves and deep-sclerectomy all work in the same way. They are all “bleb-dependent surgery” utilising a bleb, or fistula, which leaks under the conjunctiva draining aqueous away from the sub-conjunctival space, via the subconjunctival blood vessels. This makes them susceptible to bleb failure, from fibrosis, or you run the risk of bleb leakage, and possible endophthalmitis, following the use of anti-metabolites”, said Clive Peckar MSc, FRCS, FRCOphth, Warrington, UK.

For that reason, some ophthalmologists favour “bleb-independent Schlemm’s canal surgery” designed to restore the natural outflow of aqueous, he told EuroTimes in an interview. Back in the 1990s Prof Robert Stegmann developed viscocanalostomy, a technique that involved the baring of Descemet’s membrane, to create a bypass of the diseased trabecular meshwork, into an intra-scleral lake, and direct drainage into a distended Schlemm’s canal, utilising high viscosity sodium hyaluronate. Whilst this technique did reduce complications, especially hypotony, it was criticised for not dropping the IOP as low as trabeculectomy.

More recently, Prof Stegmann and his associates, have introduced a variation of this technique in which a microcatheter is used to open Schlemm’s canal for the full 360 degrees, and a suture, or stent, drawn thought the canal, to hold the canal open. In a study 157 eyes underwent the canaloplasty procedure mean IOP of 15.2 mmHg with patients using a mean of 0.8 medications compared to a mean IOP of 23.8 mmHg on a mean of 1.8 medications (Lewis et al, J Cataract Refract Surg. 2011;37(4):682-90).

The FDA approved the use of iScience catheter for canaloplasty procedures in 2008. However one of the criticisms the FDA voiced against the studies conducted using the technique is the lack of a control group. Proponents of the technique maintain that the benefits of the technique and its safety advantages over trabeculectomy are so obvious as to render a prospective study virtually unethical. However, recruitment is now under way for two large FDA studies, one sponsored by iScience, to provide such a comparison. The UK National Institute for Health and Clinical Excellence regards canaloplasty as a research procedure that should be used in the context of research or formal prospective data collection.

The future of glaucoma treatment may take an entirely new direction as genome-wide association studies continue to make progress towards discovering the ultimate cause of disease. The studies involve the comparison of the entire genome of large populations of glaucoma patients with large populations of individuals without the disease and identifying slight variations from the normal gene sequence called single nucleotide tide polymorphisms in the gene sequence occurring more frequently in the disease population, said Ananth Viswanathan MD, PhD, Moorfields Eye Hospital/UCL Institute of Ophthalmology, London, UK, at the 9th European Glaucoma Society Congress.

The studies so far suggest that glaucoma’s hereditary factors involve a complex interaction of a number of genes. An Australian group has found associations between variations in optic disc size and variations in the ATOH7 gene, which appears to play a key role in retinal ganglion cell formation (Macgregor et al, Hum. Mol. Genet. 2010; 19 (13): 2716-2724), said Dr Viswanathan, who is the principal investigator for glaucoma for the Wellcome Trust Case-Control Consortium (WTCCC) a research group conducting genome-wide association studies. “I am relatively certain in the near future that we won’t be looking beyond IOP we will be looking behind IOP because a number of groups are looking at the genetic basis of intraocular pressure and I think in the near future we will see some very interesting publications to do with how IOP is determined genetically,” he added.